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PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Gunnar Leo KARUP, et al.

Docket No: Q86966

Appln. No.: 10/528,691

Group Art Unit: 1625

Confirmation No.: 4613

Examiner: Celia C. Chang

Filed: March 22, 2005

For: NOVEL RALOXIFENE ACID ADDITION SALTS AND/OR SOLVENTS THEREOF, IMPROVED METHOD FOR PURIFICATION OF SAID RALOXIFENE ACID ADDITION SALTS AND/OR SOLVATES THEROF AND PHARMACEUTICAL COMPOSITION COMPRISING THESE

DECLARATION UNDER 37 C.F.R. § 1.132

MAIL STOP AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Erik Fischer, hereby declare and state:

THAT I am a citizen of Denmark;

THAT I have received the degree of M.Sc. Chemistry in 1994 from the University of Copenhagen;

THAT I was employed as a scientist at Medico Chemical Laboratory/Riso National Laboratory in Denmark from February 1995 to October 1995;

THAT I was employed as a researcher at Novo Nordic A/S from November 1995 to January 1998; – PRESENT

THAT I have been employed AT LEO PHARMACEUTISKE FABRIK (NOW PHARMAZELLAIS) THE LAST 9 YEARS AS HEAD OF CHEMICAL DEVELOPMENT
CORRECTION MADE 02.07.2009

THAT as a result of the newest development within the area of analysis techniques, the compound identified as raloxitene D,L-lactate hemihydrate may not in fact be the hemihydrate

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and the compound identified as raloxifene L-lactate ¼-hydrate may not in fact be the ¼-hydrate; and

THAT the following analyses supports this finding.

Table 1. Identifiers for newly prepared samples

Sample	Identifier used in this document
Raloxifene D,L-lactate	# 6.4045.23.1
Raloxifene L-lactate	# 6.4045.24.1

CRYSTALS WERE PREPARED STARTING OUT WITH RALOXIFENE OF A MUCH HIGHER PURITY TO REPRODUCE

the putative D, L-lactate hemihydrates or L-lactate ¼-hydrates of the raloxifene lactic acid addition salts. These crystals were then subjected to a moisture sorption/desorption analysis (using a SPS-11 moisture sorption analyzer, MD Messtechnik, Ulm, Germany), followed by a X-ray powder diffraction (XRPD) analysis (using a Siemens D-5000 diffractometer, Bruker-AXS, Karlsruhe, Germany). In the sorption/desorption analysis it was found that the D, L-lactate showed distinctive features of an anhydrate. The compound adsorbed water up to about 0.0 mol water per mol raloxifene lactate (Fig. 1) upon increase of the relative humidity, and when the relative humidity was lowered, no significant hysteresis was observed. This behavior indicates that the water molecules do not form part of the crystal structure. Likewise the L-lactate form of raloxifene adsorbed up to 0.28 mol water per mol raloxifene lactate (Fig. 2) without any hysteresis during the analysis.

CORRECTION MADE 02.09.2007

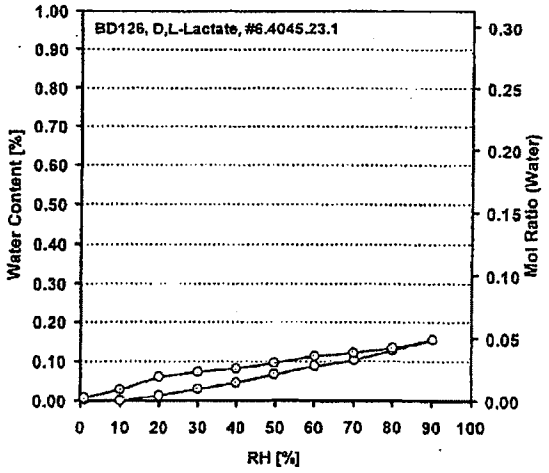

Fig. 1. Sorption/desorption isotherm for newly prepared raloxifene D, L-lactate

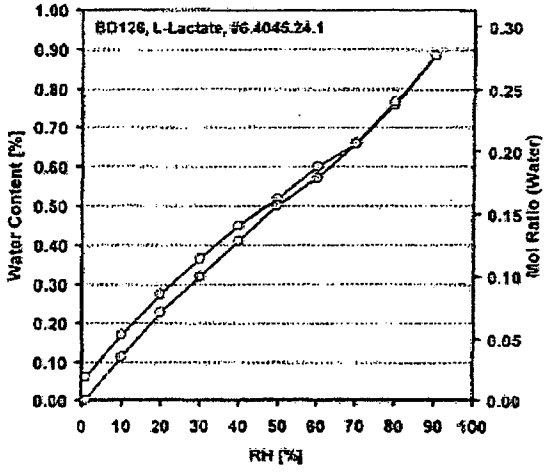

Fig. 2. Sorption/desorption isotherm for newly prepared raloxifene L-lactate

The subsequent XRPD-analysis revealed that the diffractogram of the D, L-lactate (Fig. 3 of this document) showed very good compliance with the diffractogram shown in Fig. 2 of the present application, and that of the L-lactate (Fig. 4 of this document) was in compliance with

the diffractogram of Fig. 6 of the present application. The arrows in Fig. 3 point to two minor differences thought to represent impurities in the analyzed sample.

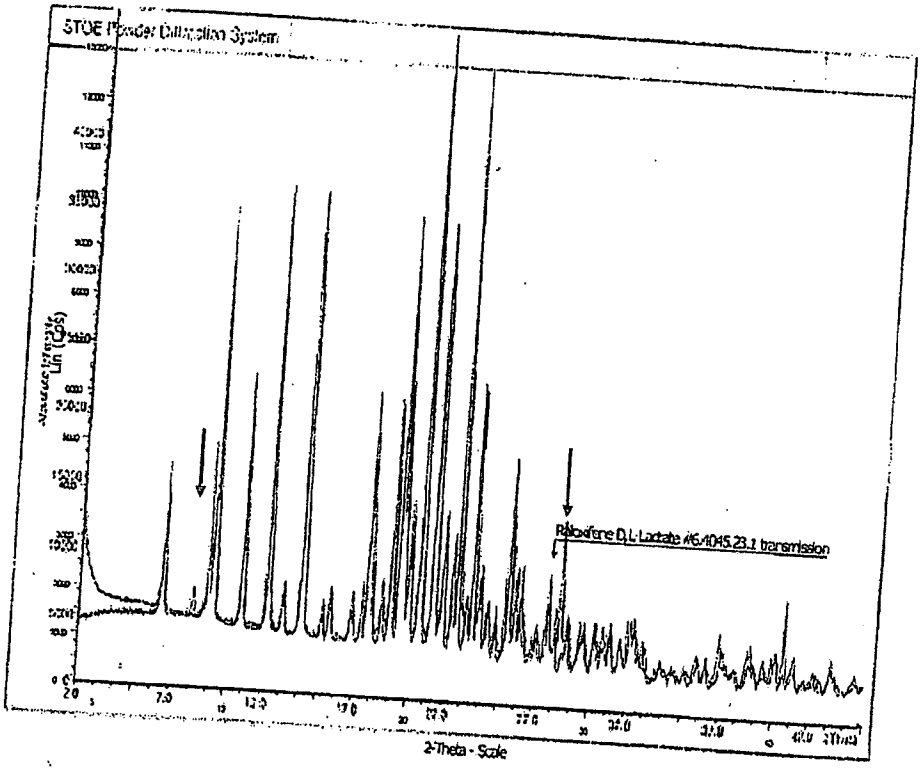

Fig. 3. Superimposition of XRPD-diffractogram of newly prepared raloxifene D,L-lactate (#6.4045.23.1) with Fig. 2 of patent application 10/528,691).

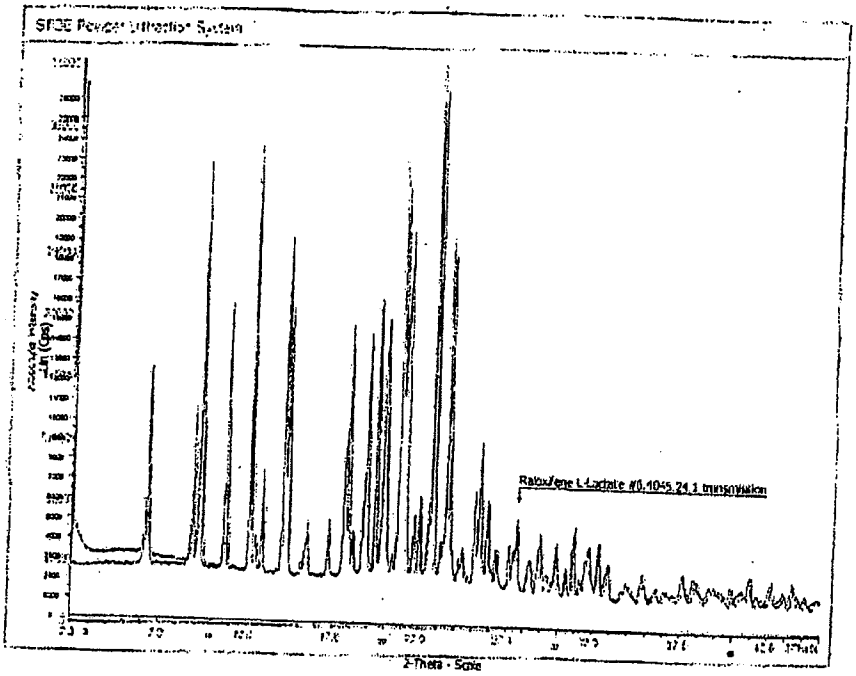

Fig. 4. Superimposition of XRPD-diffractogram of newly prepared raloxifene L-lactate (# 6.4045.24.1) with Fig. 2 of patent application 10/528,691.

It is well known that precipitation of the same organic solvents may result in different crystal chemical composition. It is also known that which contain solvent as part of the crystal cases the patterns will be expected to differ intensities for all signals. Therefore, if XRPD patterns are identical, the samples must be of identical crystalline structure and hydratization.

In view of the updated analytical data for the D, L-lactate and the L-lactate forms of raloxifene it is evident that the compounds described and claimed as "D, L-lactate hemihydrate" or "L-lactate ¼ -hydrate" in the present application must have been anhydrous, as no such crystal forms seem to exist for raloxifene.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that

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these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 02.07.2009